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10/609,019	06/26/2003	Richard K. Cooper	51687-0101 (287015)	8431

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EXAMINER

SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
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1632

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/609,019

Applicant(s)

COOPER ET AL.

Examiner

Anoop Singh

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 and 52-84 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 84 is/are allowed.
- 6) ☒ Claim(s) 1-21, 52-83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
- Paper No(s)/Mail Date _____.

- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments and claims filed October 31, 2007, has been received and entered. Applicants have amended claim 1, 52, 61, 63, while claims 22-51 have been cancelled. Applicants have also added 81-84 generally directed to elected invention.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Claims 1-21, 52-84 are under examination.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1-6, 8-10, 15-17 and 52-53, 61-62 rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771-776, IDS) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS) is withdrawn in view of amendments to the claims. It is noted that applicants have included a limitation to include a viral or eukaryotic promoter. However, upon further consideration a new rejection is made and presented below.

Claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79 rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771-776, IDS) and

Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998 IDS), MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS) is withdrawn in view of amendments to the independent claims.

Claims 1-21, 52-74, 76, 78 and 79 rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771-776, IDS) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998, IDS) or MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS) and further in view of Wallace, R. A, King J.L and Sanders, G.P., (Biology: The Science of Life, 1986, Scott Foresman and Company, pp 235, IDS) is withdrawn in view of amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2, 4-6, 8-10, 12, 15-16, 17, 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl

Environ Microbiol. 1994 March; 60(3): 771-776, IDS), IDS), Schulz (Journal of Mol. Biol. , 1991, 221, 65-80, IDS), Meiss et al (Biotechniques, 2000, 29(3): 476, 478-480, IDS) , Wooddell et al (US Patent application no 2003/0143740, dated 7/31/03, effective filing date 10/15/2001).

Cooper taught a vector for inserting an exogenous gene into a chromosome of a eukaryotic cell, comprising: a) a gene encoding a bacterial transposase; b) two transposon insertion sequences recognized by the transposase c) said exogenous gene, wherein said exogenous gene is between the two transposon insertion sequences; and (d) a promoter that is operably linked to said transposase gene; wherein one of said insertion sequences is located between said transposase gene and said exogenous gene; and wherein the transposase expressed by said transposase gene will excise from said vector a fragment comprising the two transposon insertion sequences and the exogenous gene between the two transposon insertion sequences, and will insert the excised fragment into a chromosome of a eukaryotic cell (claim 1, columns 27-28). Cooper describes the transposase as derived from Tn/10 (column 2, line 43; and column 8, line 58), hence it is a bacterial transposase, that is under the control of a modified promoter (column 8, line 43). In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector. The claims require a modified transposase gene, wherein two to ten codons, are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to express transgenes in various vertebrates as evidenced by the teachings in column 9, in lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG (SEQ ID no: 13) or wherein the promoter is a viral or eukaryotic promoter.

Wooddell et al provided guidance with respect to use of viral or eukaryotic promoter and polyA with a prokaryotic transposase (Tn5). It is noted that Wooddell exemplified Tn5 transposase in mammalian expression vector resulting in plasmid pMIR86 (pCMV-tn5) for stable integration into the eukaryotic cells (see para. 80-84 and example in the specification). However, Wooddell et al differed from claimed invention by not disclosing a prokaryotic transposase gene wherein that is modified to include a Kozak sequence.

However, at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention was made that an expression cassette may comprise gene of interest in operable linkage with one or more than one promoter. Prior to instant invention, it was generally known in the art that initiation codon of a prokaryotic gene such as one disclosed by Williamson would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. It is noted that most of the prior art generally teaches that initiation of eukaryotic mRNA translation occur exclusively at AUG Codons (see page 773, col. 1, last para). Williamson teaches modifying the 5' end of a prokaryotic gene to include a eukaryotic start codon, the Kozak expression start site consensus sequence to facilitate manipulation of the gene (see abstract and entire article). Williamson et al teach expression of the prokaryotic gene lysostaphin and processing of the precursor to produce active secreted enzyme in eukaryotic system. However, Williamson differed from claimed invention by not teaching prokaryotic transposase gene that is codon optimized.

Prior to instant invention, modifications of the codons for the first several N-terminal amino acids of the transposase, wherein the nucleotide at the third base position of each codon without changing the corresponding amino acid to facilitate increase transcription of the transposase gene was known. For instance, Schulz et

al disclose that if there is a low level of unregulated transcription initiation at non promoter site or inefficient transcription then unregulated read through transcript would be made resulting in decrease control of gene expression (see page 65, col. 1, para. 1). It is noted that Schulz describes that cells containing prokaryotic transposase insertion sequences synthesize low level of transposase protein. Schultz et al disclose formation of read through transcripts which are translated poorly. Schultz et al specifically discloses mutations that increase translation initiation of transposase gene from read through transcripts by potentially destabilizing the potential RNA secondary structure in ribosome binding site (see abstract). Schultz differed from claimed invention by not disclosing the vector comprising a prokaryotic transposase.

However, at the time the claimed invention was made inclusion of Kozak sequence and expression cassette that may comprise more than one gene of interest in operable linkage with more than one promoter was known. For example, Meiss et al taught a vector for providing expression of a gene of interest in either prokaryotic or vertebrate cells. The vector comprised a CMV promoter in operable linkage with a Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag. The vector also comprised a T7 promoter in operable linkage with bacterial ribosome binding site and Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag. In addition, since the reporter gene and histidine tag coding sequences are different they are interpreted to read on two separate genes of interest, which are operably linked to two different promoters as taught in the vector of Meiss et al. See Figure 1, in panel B on page 476 and also throughout pages 478 and 480. Meiss further discusses use of a CMV promoter/enhancer system.

Accordingly, in view of the teachings of Cooper, Williamson, Wooddell, Shultz and Meiss, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a

Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. Cooper had already taught a method to use transposase based vector for inserting an exogenous gene into a chromosome of a eukaryotic cell using a gene encoding a bacterial transposase and two transposon insertion sequences recognized by the transposase wherein said exogenous gene is between the two transposon insertion sequences (*supra*), while Meiss provided guidance with respect to expression cassette that may comprise more than one gene of interest in operable linkage with more than one promoter. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. One of ordinary skill in the art would have been sufficiently motivated to position Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson. In addition, It is evident that the person of ordinary skill would have optimized the expression level by substituting the promoter disclosed by Cooper to one taught by Wooddell as a matter of design choice with reasonable expectation of achieving predictable results in eukaryotic cells . Furthermore, one who would have studied Shultz would be sufficiently motivated to modify plurality of first few codons to facilitate increased transcription. In addition, nucleotide substitution that does not alter the amino acid sequence of an encoded protein due to the degeneracy of the genetic code that usually involved the third base (wobble position) of codons was also known as routine optimization to obtain optimal expression. One of ordinary skill in the art would have been sufficiently aware of these routine codon optimization processes and would have positioned Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson, Shultz and Meiss.

One who would practiced the invention would have had reasonable expectation of success because Williamson et al had already described use of Kozak sequence to express transposase gene in eukaryotic system. Williamson et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells, while Schultz provided guidance with respect to mutations in transposase gene that increase translation initiation of transposase gene from read through transcripts by potentially destabilizing the potential RNA secondary structure in ribosome binding site. Given that prior art teaches viral or eukaryotic promoter function well with prokaryotic transposase gene for expressing in eukaryotic system it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter and further optimize the codon as per the requirement of transgene and host cell as per the teaching of Shultz, Williamson and Meiss.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 7-11, 15-21, 52-53, 54 57-62, 73-74, 76 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771-776, IDS), IDS), Schulz (Journal of Mol. Biol. , 1991, 221, 65-80) , Wooddell et al (US Patent application no 2003/0143740, dated 7/31/03, effective filing date 10/15/2001), Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480, IDS) as applied to claims 1-2, 4-6, 8-10, 12, 15-17, 81 above, and further in view of Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998 IDS) or MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS).

The combined teachings of Cooper, Williamson et al, Wooddell, Schultz and Meiss have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches advantage of using ovalbumin or other egg directing sequences.

MacArthur et al teach vector comprising the control elements that include an enhanced promoter directing the expression of the transgene in the oviduct, an untranslated region 5' to the structural gene (coding region) of appropriate length and sequence to promote efficient translation, and a signal sequence directing the secretion of the transgene product in the egg white (col.3, lines 1-6). MacArthur et al teach the promoter may be ovalbumin, lysozyme, conalbumin and ovomucoid promoters and combinations thereof (See col. 7, lines 30-40). It is noted that MacArthur et al cite a number of references (see Gaub et al and others, col. 7, lines 5-30, also publicly available as GenBank accession number J00895, M24999, bp 2996-3148 has 100% homology with 4960-5112 of SEQ ID No: 3) to indicate that ovalbumin promoter is well characterized and its sequence including 8 Kb regulatory region is known in prior art. Therefore, recitation of specific sequences comprising ovalbumin promoter and signal sequence was disclosed in prior art meeting the limitation of claims 19-20, 21, 59-60, 68-69. MacArthur et al also contemplate that the control sequences include a promoter directing the expression of the transgene in the liver and a signal sequence directing the uptake and secretion of the transgene product into the egg yolk using promoter such as vitellogenin or combinations thereof (see col. 7, lines 40-45). MacArthur et al disclose control elements, which flank the transgene, include promoters and enhancers that could be used (col. 4, lines 64-65) including tissue-specific promoters. MacArthur et al teach that the vector's 5' untranslated region (UTR) very closely resembles that of ovalbumin RNA with only difference is a one base mutation near the 5' end which was necessary for construction and a 77 base leader is more consistent with Kozak's that is required for maximum translational efficiency. It is

noted that MacArthur et al contemplated any UTR with a functional sequence around the start codon could be used for enhancing translational efficiency (See col. 9, lines 1-9). MacArthur et al disclose use of standard stop codons and the polyadenylation signal are included 3' to the structural gene (See col. 9, line 53-55). It is also noted that MacArthur et al emphasize the usefulness of providing gene to an avian or chicken cell, wherein the gene is expressed in the hen's oviduct and secretion of the gene product is in the hen's eggs. However, MacArthur et al do not disclose using ovalbumin or any other promoter with prokaryotic transposase gene.

Prior to instant invention, use of control elements that included promoters was generally routine in the art. Hackett et al disclose variety of promoters that could be used including constitutive promoters, tissue-specific promoters, and inducible promoters (column 12, lines 35-40) to express transgene. It is also noted that Hackett also contemplates a particular DNA sequence could be modified to employ the codons preferred for a particular cell type. In addition, Hackett et al also disclose different nucleic acid encoding protein including growth hormone and insulin comprising a promoter such as ovalbumin promoter that could direct expression of transgene for the production of recombinant protein in milk, urine, blood or eggs (column 16, lines 20-45). Furthermore, Hackett et al also disclose tagging of an exogenous gene and teach isolating the tagged gene (see example 7 and 8).

Accordingly, in view of the teachings of Cooper, Williamson, Wooddell, Schultz and Meiss, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper, Wooddell and Schultz by substituting the viral promoter with other constitutive promoters, tissue-specific or inducible promoters disclosed by MacArthur et al or Hackett such that the modified promoter is in operable linkage with a prokaryotic transposase gene with reasonable expectation of success. Given that one of ordinary skill in the art would have known that any initiation codon of a prokaryotic gene

would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence and that viral or eukaryotic promoters work well with prokaryotic transposase as per teaching of Williamson and Wooddell it would have been obvious for one of ordinary skill to modify the vector to include a Kozak sequence, with a reasonable expectation of success. One of ordinary skill in the art could have combined the elements as claimed by known methods with no change in their known function and the combination would have yielded predictable result in directing the expression of the transgene in the liver and a signal sequence directing the uptake and secretion of the transgene product into the egg yolk using promoter such as vitellogenin or other combinations. It is emphasized that changing codon by individually modifying wild type sequence of C or G at third base position of the codon to A or T would have been obvious and routine optimization depending upon transgene and host species to facilitate increased transcription by destabilizing the secondary RNA structure in ribosome and strand dissociation.

One who would practiced the invention would have had reasonable expectation of success because MacArthur/ Hackett had already described that signal sequence and promoters that could be used to direct expression of the transgene in milk or egg. Wooddell, Williamson and Meiss had already described use of viral or eukaryotic promoter, Kozak sequence to express prokaryotic transposase gene in eukaryotic cells. Thus, it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter such as ovalbumin or other egg directing sequences to direct expression of the gene in egg.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 3, 13-14, 55-56, 57-72, 77, 78 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771-776, IDS), Schulz (Journal of Mol. Biol. , 1991, 221, 65-80) and Wooddell et al (US Patent application no 2003/0143740, dated 7/31/03, effective filing date 10/15/2001), Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480, IDS), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998 IDS) or MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS) as applied to claims 1-2, 4-12, 15-21, 52-54, 57-62, 73-74, 76, 81-82 above and further in view of Jeltsch et al (Eur. J. Biochem. 1982, 122, 291-295)/NCBI accession no Y00407 and Wallace, R. A, King J.L and Sanders, G.P., (Biology: The Science of Life, 1986, Scott Foresman and Company, pp 235, IDS).

The combined teachings of Cooper, Williamson et al, Wooddell, Shultz, Meiss and MacArthur /Hackett have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches using conalbumin Poly A with prokaryotic gene and two-stop codon.

It is noted that Jeltsch et al (also in Genbank accession no Y00407) provided guidance with respect to conalbumin mRNA containing 2376 nucleotide. Jeltsch et al cite to disclose 5' and 3' untranslated region (see page 292, col.2, para. 2) meeting the limitation of claim 13, 55, 71 and 77. Jeltsch et al also teach the common eukaryotic PolyA signal (see figure 2). Jeltsch et al differed from claimed invention by not disclosing use of conalbumin Poly A with a prokaryotic gene.

Prior to filing of this application, Wallace et al teach three stop codons UAA, UAG and UGA that are used as stop codon. It is noted that Wallace et al also disclose use of double stop codon such as UAA-UAG to ensure message to ribosome (pp 235, col. 2, see section) polypeptide chain termination.

Accordingly, it would have been obvious and within the scope of skill for an artisan to subject the vector taught by Cooper, Williamson, Wooddell, Schultz,

Meiss and MacArthur /Hackett to include two-stop codon operably linked to the transposase as taught by Wallace. Wooddell had already taught use of standard stop codons and the polyadenylation signal in order to express transposase gene. It would have been prima facie obvious that all the claimed elements were known in prior art and one of ordinary skill in the art would could have combined the elements as claimed by known methods with no change in their respective functions and combination would have yielded predictable result of optimal expression of prokaryotic transposase gene. One of ordinary skill in the art would have included multiple-stop codon to ensure proper termination of transposase synthesis and would have also included other poly A as a matter of design choice as obvious modification for optimal expression in mammalian system as exemplified by Wooddell. It is noted that Jeltsch et al provided guidance with respect to mRNA sequence of conalbumin and also discloses untranslated region. Furthermore, conalbumin Poly A broadly encompasses PolyA or any signal and does not require entire non-coding region of a conalbumin for instant rejection.

One who would practiced the invention would have had reasonable expectation of success because Wooddell , Wallace had already described use of Poly A and two stop codon to ensure polypeptide chain termination respectively. It would have only required routine experimentation to modify the vector to include two stop codons operably linked to the gene to enhance the termination of transposase synthesis. Claims 3 and 83 are included in the rejection because combination of art teaches one of ordinary skill in the would have modified the vector of Cooper to include known elements comprising CMV promoter that is modified by addition of ACC sequence upstream of ATG taught by references of Wooddell in view of Williamson and Schultz, Tn10 disclosed by Cooper, synthetic poly A (Wooddell and also commercially available through Gene therapy system, CA) and stop codon (Wallace) with no change in their respective functions as claimed and combination

of these known elements would have yielded predictable result of optimal expression of prokaryotic transposase gene in eukaryotic system.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Claims 79, 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771-776, IDS), Schulz (Journal of Mol. Biol. , 1991, 221, 65-80) and Wooddell et al (US Patent application no 2003/0143740, dated 7/31/03, effective filing date 10/15/2001), Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480, IDS), Jeltsch et al (Eur. J. Biochem. 1982, 122, 291-295) and Wallace, R. A, King J.L and Sanders, G.P., (Biology: The Science of Life, 1986, Scott Foresman and Company, pp 235, IDS) as applied to claims 1-21, 55-74, 76-78, 81-83 above and further in view of Hu et al (US patent no. 6939959, dated 10/28/05, effective filing date 10/26/2001) and Dobeli et al (Protein Expression And Purification 12, 404-414, 1998)

The combined teachings of Cooper, Williamson et al, Wooddell, Shultz, Meiss, MacArthur /Hackett, Jeltsch et al and Wallace have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches using TAG sequence for protein purification.

Prior to instant invention use of TAG sequence that is linked to the gene in a vector to facilitate separation of the signal sequence from the peptide of interest was routine commercially available in prior art. The TAG sequence allows one of ordinary skill in the art to isolate the protein using column purification or use to include a cleavage site to remove the desired protein from the signal and purification sequences. For instance, Hu et al describe use of antigenic epitopes that facilitate affinity detection and isolation of the polypeptides including poly-His

or other antigenic peptide epitopes exemplified in Patent 5,011,912. 20, while Dobeli provided guidance with respect to an epitope that is located in the gp41 protein of HIV and consists of a the gp41 protein and consists of a stretch of 22–36 amino acids containing an intramolecular disulfide bridge wherein a loop is formed by 5 amino acids between the two cysteines and represents a conformational epitope as described above.

Accordingly, it would have been obvious and within the scope of skill for an artisan to subject the vector taught by Cooper, Williamson, Wooddell, Schultz, Meiss and MacArthur /Hackett to include TAG sequence as disclosed by Hu et al. It would have been prima facie obvious to one of ordinary skill in the art to include TAG sequence as a matter of design choice since TAG sequence including use of hairloop domain of HIV gp41 or any other antigenic epitope were known in prior art and one of ordinary skill in the art would could have combined the TAG sequence using the known methods with no change in their respective functions and combination would have yielded predictable result to facilitate separation of the signal sequence from the peptide of interest. One who would practiced the invention would have had reasonable expectation of success because it was routine to use antigenic epitope as TAG sequence to separate the signal sequence from the peptide of interest. It would have only required routine experimentation to modify the vector to include TAG sequence.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Response to Arguments

Applicant's arguments filed on October 31, 2007 have been fully considered but are moot in view of new grounds of rejection. Instant response to arguments is presented to the extent they apply to new grounds of rejection.

Applicant's arguments with respect to claims 1-21, 52-84 has been fully considered but they are not persuasive.

Applicants argue that as amended, the claimed vectors include a viral or eukaryotic promoter driving expression of the prokaryotic transposase gene and none of the references describe, teach or suggest using a eukaryotic promoter (see page 12 of the argument).

In response, Contrary to applicant's argument Wooddell et al provided guidance with respect to use of viral or eukaryotic promoter and polyA with a prokaryotic transposase (Tn5). Specifically, Wooddell exemplified Tn5 transposase in mammalian expression vector resulting in plasmid pMIR86 (pCMV-tn5) for stable integration into the eukaryotic cells (see para. 80-84 and example in the specification).

Applicants assert that the cited references do not describe each and every element of the claimed invention. Also, none of the references describe or suggested a transposase modified such that a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein are individually modified from the wild-type sequence of cytosine or guanine at the third base position of the codon to an adenine or a thymine, such that the modification does not change the amino acid encoded by the modified codon. Applicants argue the optimization of codon usage that is described by Savakis et al. is distinct from Applicants' modification of the N-terminal first 10 codons to replace C or G at the wobble position with A or T. Applicants are not modifying the transposase to

optimize codon usage for a particular host, but to increase strand dissociation during transcription (see page 13 of the argument).

It appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention of a vector comprising a prokaryotic gene and claimed embodiments of modified prokaryotic transposase gene. It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979).

Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole.

In the instant case, independent claim 1 requires 3 basic elements in prior art 1) a prokaryotic transposase gene operably linked to a promoter wherein 2) the 3' end of the viral or eukaryotic promoter comprising a Kozak sequence to include first codon of the transposase gene and wherein 3) transposase gene is modified such that plurality of codon of the transposase gene that encodes amino acid 2-10 are modified from C or T to A or T at third position of the codon without changing the amino acid encoded by the modified codon.

Cooper et al disclose the vector comprising a gene encoding a prokaryotic transposase operably linked to a promoter; and an exogenous gene located between the transposon insertion sequences. The promoter directing expression of the transposase gene may be inducible. See the claims. In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to express transgenes in various vertebrates as evidenced by the teachings in column 9, in

lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences. With respect to using a viral or eukaryotic promoter, one of ordinary skill in the art would have substituted a viral or eukaryotic promoter as a matter of design choice to optimize the expression of prokaryotic transposase gene in eukaryotic system particularly since Wooddell taught viral or eukaryotic promoter and polyA work with a prokaryotic transposase (Tn5) in mammalian expression vector for stable integration into the eukaryotic cells.

With respect to applicants argument of a modified transposase gene, wherein two to ten codons, are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon (See argument 13 and 14). Examiner has provided references of Schulz et al disclose that if there is a low level of unregulated transcription initiation at non promoter site or inefficient transcription then unregulated read through transcript is made resulting in decrease control of gene expression (see page 65, col. 1, para. 1). It is noted that Schulz describes that cells containing prokaryotic transposase insertion sequences synthesize low level of transposase protein. Schultz et al disclose formation of read through transcripts which are translated poorly. Schultz et al specifically discloses mutations that increase translation initiation of transposase gene from read through transcripts by potentially destabilizing the potential RNA secondary structure in ribosome binding site (see abstract). Schultz differed from claimed invention by not disclosing the vector comprising a prokaryotic transposase. Prior to instant invention, it was also known in the art that initiation codon of a prokaryotic gene such as one disclosed by Williamson would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. The reference is included to demonstrate that modification of

prokaryotic gene for expression in eukaryotic system required modification of transgene by inclusion of Kozak sequence at transcription initiation site. It is apparent from the preceding analysis that claimed embodiments were known in prior art and one of ordinary skill in the art would have studied Cooper, Wooddell, Schulz, Williamson and Meiss to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that it is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. In addition, use of Kozak sequence to initiate transcription of a transgene was known to one of ordinary skill in the art. It is emphasized that contrary to applicant's argument based on the teaching of Schulz one of ordinary skill in the art would be aware that cells containing prokaryotic transposase insertion sequences synthesize low level of transposase protein due to formation of read through transcripts which are translated poorly. Schultz et al specifically discloses mutations that increase translation initiation of transposase gene from read through transcripts by potentially destabilizing the potential RNA secondary structure in ribosome binding site. One who would have studied Schultz would be aware that nucleotide substitution that does not alter the amino acid sequence of an encoded protein due to the degeneracy of the genetic code that usually involved the third base (wobble position) of codons was also known as routine optimization to obtain optimal expression. Furthermore, contrary to applicant's assertion, most of the prior art generally teaches that initiation of eukaryotic mRNA translation occur exclusively at AUG Codons and Williamson teach modifying the 5' end of a prokaryotic gene to include a eukaryotic start codon, the Kozak expression start site consensus sequence to facilitate manipulation of the gene (see abstract and entire article, see page 773, col. 1, last para). The reference is included to demonstrate that

modification of prokaryotic gene for expression in eukaryotic system required modification of transgene by inclusion of Kozak sequence at transcription initiation site. It is apparent from the preceding analysis that claimed embodiments were known in prior art and one of ordinary skill in the art would have been sufficiently aware of these routine codon optimization processes and would have positioned Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson. In addition, It is evident that the person of ordinary skill would have optimized the transposase gene to direct expression of different gene of interest by individually modifying wild type sequence of CG at third base position of the codon to A or T.

Applicant's arguments that there is no motivation or reason to combine (see page 15 of the argument) Cooper with Savakis et al. and Williamson et al. to arrive at Applicants' invention are moot as new rejection includes references that specifically provide guidance for one of ordinary skill in the art to modify the transposase gene disclosed by Copper in view of teaching of Wooddell, Schulz, Meiss and Williamson to arrive to claimed invention with reasonable expectation of success.

Applicants argue that neither MacArthur et al, nor Hackett et al., disclose or suggest the use of eukaryotic or viral promoters nor signal sequences with a prokaryotic transposase (see page 16 of the argument). Applicants assert that MacArthur et al. does not describe transposon-based vectors, but describes retroviral vectors. The promoters, signal sequences, and other control sequences described by MacArthur et al. are only used with the exogenous gene and are not used to control expression of a prokaryotic gene (e.g., a prokaryotic transposase) in a eukaryotic cell. Thus, there is no teaching in MacArthur et al. of how to use such sequences with a prokaryotic transposase gene as recited in Applicants' claims and no reason to expect that the use of such eukaryotic control sequence could be used

in combination with a prokaryotic transposase.

In response, it is noted that rejection of record includes reference of Wooddell et al that discloses use of viral or eukaryotic promoter and polyA with a prokaryotic transposase (Tn5). Specifically, Wooddell exemplified Tn5 transposase in mammalian expression vector resulting in plasmid pMIR86 (pCMV-tn5) for stable integration into the eukaryotic cells (see para. 80-84 and example in the specification). One of ordinary skill in the art would have used any viral, eukaryotic or other egg directing sequence disclosed by Wooddell, MacArthur et al or Hackett as a matter of design choice with reasonable expectation of success in achieving predictable result to stably express modified prokaryotic gene in eukaryotic system.

Applicants' argument of MacArthur as providing a suggestion, description or motivation to use polyA sequences with a prokaryotic gene is moot in view of new grounds of rejection (see pages 18 and 19 of the argument, supra).

Secondary considerations:

With respect to applicant's argument of unexpected result, it is emphasized that Examiner is not raising the issue of efficiency of the vector claimed in the instant application. Examiner has previously indicated that cited reference of Cooper (US patent 5,719,055) and other existing vector for avian transgenesis had poor integration frequency and it was art recognized goal to improve the efficiency of the vector. Examiner has cited new references to show it would have been prima facie obvious for one of ordinary skill in the art to modify the vector disclosed in prior art to include Kozak sequence and individually modify plurality of first few codons codon 2-10 of the wild type sequence of CG at third base position of the codon to A or T since art teaches that mutations that increase translation initiation of transposase gene from read through transcripts by potentially destabilizing the potential RNA secondary structure in ribosome binding site. In addition, nucleotide substitution that does not alter the amino acid sequence of an encoded protein due to the degeneracy of the genetic code that usually involved the third base (wobble

position) of codons was also known as routine optimization. The declaration filed m Sept. 26, 2006 shows the use of a vector (pTN mod) with a monoclonal antibody encoded by the gene of interest resulted in very high efficiency. Furthermore, applicants also assert that instant vector enables vectors to transfect cells in a live animal to produce chimeric animal. In response, it is noted that exemplified vector in the Declaration uses a specific modification, promoter and regulatory control sequence which is different from one broadly recited in the independent claims. In absence of any specific embodiments, and open ended language for using various known promoter and other sequences, it would have been obvious for one of ordinary skill in the art to try to optimize the existing vector comprising prokaryotic gene to increase its efficiency in eukaryotic system. Additionally, see MPEP §716.02(d) which states, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In the instant case, claimed embodiments are broad and are not commensurate in scope with that which Applicants argue is unexpected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21, 73-75, 79-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite to the extent the scope of claims 1(b) and (c) is unclear as they essentially recite the similar embodiments of "...wherein one or more gene of interest and their operably linked promoters are flanked by insertion sequence

recognized by transposase encoded by the modified transposase gene". Deletion of this limitation from claim 1 (b) would obviate the basis of this rejection. Claims 2-21, 73-75, 79-80 and 81 are included in the rejection as they directly or indirectly depend on claim 1. Appropriate correction is required.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Claims 75 and 84 are free of art.

US Patent application 20040142475 by Barman et al describes pgWiz vector (Gene Therapy Systems, San Diego, California) which is commercially available. It is noted that many specific elements such as CMV promoter/enhancer and PolyA sequence used in the vector comprising SEQ ID NO: 1 is derived from this plasmid.

GenBank accession number J00895 M24999, GenBank accession # S82527.1 (nt1 -675 of chicken ovalbumin enhancer-SEQ ID NO: 37) .

Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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